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APPLICATION NUMBER: ***60/487,064***
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CD DISK IS THE APPLICATION FOR THE ABOVE REFERNECED INFORMATION

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Certifying Officer

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Pharmaceutical Compositions

INCORPORATION BY REFERENCE

The content of US Patent Application No. 60/451,213 filed on February 28, 2003 is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to co-crystal api-containing compositions, pharmaceutical compositions comprising such apis, and methods for preparing the same.

BACKGROUND OF THE INVENTION

Active pharmaceutical ingredients (api or apis (plural)) in pharmaceutical compositions can be prepared in a variety of different forms. Such apis can be prepared so as to have a variety of different chemical forms including chemical derivatives or salts. Such apis can also be prepared to have different physical forms. For example, the apis may be amorphous or may have different crystalline polymorphs, perhaps existing in different solvation or hydration states. By varying the form of an api, it is possible to vary the physical properties thereof. For example, crystalline polymorphs typically have different solubilities from one another, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapour pressure, density, colour, and compressibility. Accordingly, variation of the crystallinic state of an api is one of many ways in which to modulate the physical properties thereof.

It would be advantageous to have new forms of these apis that have improved properties, in particular, as oral formulations. Specifically, it is desirable to identify improved forms of apis that exhibit significantly improved properties including increased aqueous solubility and stability. Further, it is desirable to improve the processability, or preparation of pharmaceutical formulations. For example, needle-like crystal forms or habits of apis can cause aggregation, even in compositions where the api is mixed with other substances, such that a non-uniform mixture is obtained. It is also desirable to

increase the dissolution rate of api-containing pharmaceutical compositions in water, increase the bioavailability of orally-administered compositions, and provide a more rapid onset to therapeutic effect. It is also desirable to have a form of the api which, when administered to a subject, reaches a peak plasma level faster, has a longer lasting therapeutic plasma concentration, and higher overall exposure at high doses when compared to equivalent amounts of the api in its presently-known form.

SUMMARY OF THE INVENTION

It has now been found that new co-crystalline forms of apis can be obtained which improve the properties of apis as compared to the apis in a non-co-crystalline state (free acid, free base, zwitter ions, salts, etc,).

Accordingly, in a first aspect, the present invention provides a co-crystal pharmaceutical composition comprising an api compound and a co-crystal forming compound, such that the api and co-crystal forming compound are capable of co-crystallizing from a solid or solution phase under crystallization conditions.

Another aspect of the present invention provides a process for the production of a pharmaceutical composition, which process comprises:

(1) providing an api which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(2) providing a co-crystal forming compound which has at least one functional group selected from ether, thioether, alcohol, thiol, aldehyde, ketone, thioketone, nitrate ester, phosphate ester, thiophosphate ester, ester, thioester, sulfate ester, carboxylic acid, phosphonic acid, phosphinic acid, sulfonic acid, amide, primary amine, secondary amine, ammonia, tertiary amine, sp2 amine, thiocyanate, cyanamide, oxime, nitrile diazo, organohalide, nitro, s-heterocyclic ring, thiophene, n-heterocyclic

ring, pyrrole, o-heterocyclic ring, furan, epoxide, peroxide, hydroxamic acid, imidazole, and pyridine;

(3) grinding, heating or contacting in solution the api with the co-crystal forming compound under crystallization conditions, and

(4) isolating co-crystals formed thereby; and

(5) incorporating the co-crystals into a pharmaceutical composition.

A further aspect of the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) grinding, heating or contacting in solution an api compound with a co-crystal forming compound, under crystallization conditions, so as to form a solid phase;

(2) isolating co-crystals comprising the api and the co-crystal forming compound.

In a further aspect, the present invention provides a process for the production of a pharmaceutical composition, which comprises:

(1) providing (*i*) an api or a plurality of different apis, and (*ii*) a co-crystal forming compound or a plurality of different co-crystal forming compounds, wherein at least one of the api and the co-crystal forming compound is provided as a plurality thereof;

(2) isolating co-crystals comprising the api and the co-crystal forming compound.

Solubility Modulation:

In a further aspect, the present invention provides a process for modulating the solubility of an api, which process comprises:

(1) grinding, heating or contacting in solution the api with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the api and the co-crystal forming compound;

(2) isolating co-crystals comprising the api and the co-crystal forming compound.

Dissolution Modulation:

In a further aspect, the present invention provides a process for modulating the dissolution of an api, whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased or decreased,which process comprises:

(1) grinding, heating or contacting in solution the api with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the api and the co-crystal forming compound;

(2) isolating co-crystals comprising the api and the co-crystal forming compound.

In a preferred embodiment, the dissolution of the api is increased.

Bioavailability Modulation:

In a further aspect, the present invention provides a process for modulating the bioavailability of an api, whereby the AUC is increased, the time to T_{max} is reduced, the length of time the concentration of the api is above ½ T_{max} is increased, or C_{max} is increased,which process comprises:

(1) grinding, heating or contacting in solution the api with a co-crystal forming compound under crystallization conditions, so as to form a co-crystal of the api and the co-crystal forming compound;

(2) isolating co-crystals comprising the api and the co-crystal forming compound.

Dose Response Modulation:

In a further aspect the present invention provides a process for improving the linearity of a dose response of an api, which process comprises: